OPP OFFICIAL RECORD

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WASHINGTON, D.C. 20460

CASWELL FILE

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OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT **4-CHLOROPHENOXYACETIC ACID:** Developmental Toxicity Study in Rats. Action Code 625 **6(A(2) Registration Special Review.**

FROM: Jess Rowland, Toxicologist *Jess Rowland 6/22/92*
Section II, Toxicology Branch II
Health Effects Division (H7509C)

TO: L. Deluise / T. Luminello
Product Manager (52)
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THRU: K.Clark Swentzel, Section Head *K. Clark Swentzel 6/22/92*
Section II, Toxicology Branch II
Health Effects Division (H7509C)
and
Marcia van Gemert, Ph.D., Chief *M van Gemert 6/23/92*
Toxicology Branch II
Health Effects Division (H7509C)

PROJECT IDENTIFICATIONS: Submission: **S418640** Case #: **802264**
Chemical: 019401 **Caswell No. 204**

MRID No(s): 423226-01 [Range-finding Developmental Toxicity **Study]**
423226-02 [Main Developmental Toxicity **Study**]

Registrant: Hunt-Wesson Inc, Fullerton, CA.

ACTION REQUESTED: Review of range-finding and developmental toxicity studies in rats with 4-chlorophenoxyacetic Acid. **An earlier 6(a)(2) report [MRID NO.422443-01] was based on findings included in this report.**

RESPONSE: A Data Evaluation Report [DER] for each of the above referenced studies is attached. The **Toxicology Branch II concludes that these data meet the criteria for 6(a)(2) since the developmental effects observed in this study were not observed in studies conducted with 4-CPA and previously reported to the Agency.**

PRIMARY REVIEWER: Jess Rowland, Toxicologist
Section II, Toxicology Branch II

SECONDARY REVIEWER: K. Clark Swentzel, Section Head
Section II, Toxicology Branch II

Jess Rowland 6/22/92

K. Clark Swentzel 6/22/92

DATA EVALUATION REPORT

1. RANGE-FINDING STUDY

STUDY TYPE: Developmental Toxicity **[R-F Study]** **GUIDELINE: N/A**

CASWELL NO. 204 **MRID No. 423226-01**

TEST MATERIAL: 4-chlorophenoxyacetic acid [4-CPA]

REGISTRANT: Hunt-Wesson, Inc., Fullerton, CA

TESTING LABORATORY: Hazleton Wisconsin, Madison, WI

STUDY IDENTIFICATION: HWI-6341-100

TITLE OF REPORT: Range-Finding Teratology Study with 4-Chlorophenoxyacetic Acid in Rats.

AUTHOR: Susan M. Henwood, MS, DABT

REPORT DATE: May 14, 1992

SUMMARY: Pregnant rats were given oral administration of 4-chlorophenxoyacetic acid at oral doses of 0, 37.5, 75, 150, or 300 mg/kg/day during days 6 through 15 of gestation. Dams were sacrificed on gestation day 20. One dam was sacrificed moribund, due to dosing error at 75 mg/kg/day. 4-CPA did not induce maternal toxicity; no treatment-related effects were evident from survival, clinical signs of toxicity, mean body weight, body weight gain, or gross pathology. Treatment had no adverse effects at any dose level on pregnancy rate, pre- and post-implantation losses, the number of corpora lutea, the number of implantations, the number of resorptions or litter size. No fetal data were reported.

MATERNAL TOXICITY NOEL = 300 mg/kg/day [HDT]
LOEL = Not achieved

DEVELOPMENTAL TOXICITY = NOEL = 300 mg/kg/day [HDT]
LOEL = Not achieved

CORE CLASSIFICATION: Not applicable; range-finding study.

1. OBJECTIVE

The objective of this range-finding study, was to establish appropriate dose levels of 4-chlorophenoxyacetic acid [4-CPA] for the main study.

2. PROTOCOL

Groups of five female Crl:CD BR VAF/Plus rat [approximately 5.5 months of age and 3.5 to 4.0 kg] were given oral doses of **4-CPA [99% pure]** at doses of 0, 37.5, 75, 150 or 300 mg/kg/day in 0.5% CMC/deionized distilled water [10 mL/kg] daily, during days 6 through 15 of gestation. Concentration, homogeneity and stability of the test article/vehicle mixtures were determined prior to the initiation of the study.

Animals were observed for mortality, moribundity and clinical signs of toxicity twice daily. Dams were weighed on gestation days 0, 6, 9, 12, 16 and 20 of gestation. Dams in each group were sacrificed on day 20 and postmortem examination included macroscopic examination of internal organs, with emphasis on the uterus, uterine contents, position of each fetus in the uterus, and corpora lutea counts. Fetal examinations were not performed.

3. RESULTS

i. Analysis of dosing solution

The mean concentrations found were 98.1%, 98.4%, 95.3% and 94.3% of the nominal concentration for the 37.5, 75, 105 and 300 mg/kg/day dose groups, respectively. 4-CPA was homogeneous and stable in the CMC deionized distilled water vehicle for up to 10 days at rom temperature.

ii. Maternal Toxicity

- Except for the one dam that was sacrificed moribund on Day 14 at 75 mg/kg/day, no maternal mortality occurred during the study.

- Except for the red nasal discharge and labored breathing observed in the dam that was sacrificed moribund, no treatment-related clinical signs of toxicity were seen.

- No treatment-related effects were seen in mean body weight, body weight gain, or corrected body weight gain at any dose level.

- Except for the fluid-filled trachea and congested lungs [signs of dosing error] observed in the dam that was sacrificed moribund, necropsy revealed no treatment-related findings.

- The pregnancy rates were 100%, 80%, 80%, 100% and 100% for the 0, 37.5, 75, 150, and 300 mg/kg/day dose groups, respectively.

- Treatment had no effect on corpora lutea, implantation sites, pre-and post-implantation losses, litter size or viable fetuses at any dose level.

iii. Developmental Toxicity

No data were reported for fetal examinations.

4. CONCLUSION:

Since no maternal or developmental toxicity was seen at the highest dose tested [300 mg/kg/day], doses of 150, 300, 600 and 1000 mg/kg/day were selected for the main study, based on the LD_{50} data and the limit dose concept [1000 mg/kg/day].

Maternal Toxicity NOEL = 300 mg/kg/day [HDT]
LOEL = Not achieved

Developmental Toxicity NOEL = 300 mg/kg/day [HDT]
LOEL = Not achieved

PRIMARY REVIEWER: Jess Rowland, Toxicologist
Section II, Toxicology Branch II

Jess Rowland 6/22/92

SECONDARY REVIEWER: K. Clark Swentzel, Section Head
Section II, Toxicology Branch II

K. Clark Swentzel 6/22/92

DATA EVALUATION REPORT

MAIN STUDY

STUDY TYPE: Developmental Toxicity **[Main Study]** **GUIDELINE:** 83-3(b)

CASWELL NO. 204 **MRID No. 423226-02**

TEST MATERIAL: 4-Chlorophenoxyacetic Acid [4-CPA]

REGISTRANT: Hunt-Wesson **STUDY IDENTIFICATION:** HWI-6341-101

TESTING LABORATORY: Hazleton Wisconsin, Madison, WI.

TITLE OF REPORT: TERATOLOGY STUDY WITH 4-CHLOROPHENOXYACETIC ACID IN RATS.

AUTHOR: Susan M. Henwood, MS, DABT

REPORT DATE: May 14, 1992

SUMMARY: Groups of 25 Crl:CD BR VAF/Plus rats were given oral doses of **4 CPA [99% pure]** at 0, 150, 300, 600 or 1000 mg/kg/day during days 6 through 15 of gestation. No maternal toxicity was observed at 150 mg/kg/day. At the higher doses, maternal toxicity was manifested by mortality/morbidity [1000 mg/kg/day], clinical signs of toxicity characterized by tremors, uncoordinated movements, recumbent posture, languidness and cold to touch , and decreases in body weight gain. Treatment had no effect on the pregnancy rate, number of corpora lutea, implantations, total live fetuses, resorption rate, pre- and post-implantation losses, and fetal sex ratio. Fetal body weights were decreased at 600 and 1000 mg/kg/day. No treatment-related fetal external or fetal soft tissue abnormalities were seen at any dose level. Treatment-related skeletal variations included increased fetal and litter incidence of unossified sternebra No.5 [300-1000 mg/kg/day], seventh cervical ribs [300-1000 mg/kg/day], and misaligned sternebrae [1000 mg/kg/day]. No treatment-related skeletal malformations were seen. Based on the results of this study, the following NOELs and LOELs are established.

MATERNAL & DEVELOPMENTAL TOXICITY: NOEL = 150 mg/kg/day
LOEL = 300 mg/kg/day

CORE CLASSIFICATION: Guideline; this study satisfies the requirements for a developmental toxicity study in rats (83-3 a).

I. OBJECTIVE

The objective of this study was to assess the effects of the **4-chlorophenoxyacetic Acid [4-CPA]** on the embryonic and fetal development following oral administration to rats during the period of organogenesis.

II. MATERIALS AND METHODS

a. Test Material

Identity: 4-chlorophenoxyacetic acid
Batch No.: Not indicated
Purity: 99 - 100%
Description: White powder

b. Test Animals

Species/Sex: Female rats
Strain: Crl:CD BR VAF/Plus
Age on Gestation Day 0: Approximately 9 weeks
Weight on Gestation Day 0: 197 - 267 g
Identification: Ear tags.
Acclimation Period: 10 days.
Housing: Individually in stainless steel cages
Food: Purina Certified Rodent Chow #5002 ad libitum.
Water: Tap water ad libitum
Environment: Temperature, 72°F ± 6°; Humidity, 50 ± 20%
Light cycle, 12 hour light/dark

Group Assignment: 25 females were randomly assigned to 1 control group and 3 treatment groups.

c. Mating

Each female was paired with one male. Vaginal smears were taken daily during cohabitation, and the presence of copulatory plug or sperm in the vaginal smear was considered evidence of mating. The day this evidence was seen was designated as Day 0 of gestation, and the female was then removed from the male's cage and housed individually.

d. Preparation of Dosing Solutions

Each dose level was prepared independently in sequential order of increasing concentrations. The specific amount of test material was weighed into a container to which appropriate amount of the vehicle [0.5% CMC in deionized water] water was added, the pH of the mixture was checked, and adjusted the mixture was kept homogenous by stirring on a magnetic stirrer. Dosing solutions were prepared fresh weekly and stored at room temperature. During dosing, homogenous test material preparations were maintained using a magnetic stirrer.

e. Analysis of the Dosing Solutions

Concentration analyses was performed during weeks 1, 2 and 3. Homogeneity analyses was performed from the top, middle and bottom samples of test material suspensions prepared for the 150 and 1000 mg/kg/day groups. Stability analyses was performed on the day of mixing, 10 days at room temperature, and two weeks stored in freezer.

f. Administration of Test Article

The test article was administered daily orally via gavage at doses of 0, 150, 300, 600 or 1000 mg/kg/day during days 6 through 15 of gestation. The control group received the vehicle [deionized distilled water only. All groups received a dosing volume of 10 mL/kg body weight and the dose volumes were based on Day 6 body weights.

g. Observations

All animals were observed twice daily for mortality/moribundity and clinical signs of toxicity. A detailed physical examination was done at each body weight interval which was obtained on Days 0, 6, 9, 12, 16, and 20 of gestation. Individual food consumptions were **not** measured in this study.

h. Termination

Any animal which died, appeared moribund or showed indications of early termination of pregnancy was submitted for complete necropsy. All surviving does were sacrificed on gestation day 20, obvious gross pathologic alterations were recorded and gravid uterus was weighed.

i. Cesarean Section

The thoracic, abdominal and pelvic cavities were examined for gross lesions, and in the event of gross lesions, the tissues were preserved in neutral buffered 10% formalin. The uterus was removed from the body, examined externally, weighed and then opened for internal examination. Uteri that appeared to be from nonpregnant rats were stained with 10% ammonium sulfide to determine pregnancy status. Corpora lutea were counted, the number and placement of implantation, early and late resorption, and live and dead fetuses were recorded.

j. Fetal Examinations

Each fetus was removed from the uterus and individually weighed, and observed for gross external alterations. Every fetus was examined to determine sex and soft tissue alterations. Fetuses were then eviscerated, stained with Alizarin red-S, and examined for skeletal alterations.

k. Statistical Analysis

One-way ANOVA was used to analyze maternal body weights, body weight gains, gravid uterine weights and cesarean section data. Fetal abnormality data, when appropriate, were analyzed by the Cochran-Armitage test for trend and departure and by a Fisher-Irwin exact test. One-way ANOVA was used to analyze fetal body weight with the total number of fetuses in the litter as the covariate. The proportion of litters and fetuses with external, soft tissue, and skeletal abnormalities in the treated groups were compared with the control group by the Cochran-Armitage test for trend and departure and by a Fisher-Irwin exact test.

l. Quality Assurance Measures:

A quality assurance statement was signed and dated 05/04/91. This date conforms to the review of the study phases and the draft and the final reports.

III. RESULTS

Analysis of the Dosing Solutions

The mean concentrations of test article found were 99.3%, 99%, 99.3% and 101% of the nominal concentrations for the 150, 300, 600 and 1000 mg/kg/day doses, respectively, for study Week 1. For study Week 2, the corresponding values were 105%, 105%, 104%, and 98.9% and for study Week 3, the values were 93.3%, 97.3%, 99.3%, and 96.6%. Homogeneity ranged from 98% to 100% for the 150 mg/kg/day group and from 96.5% to 99.4% for the 1000 mg/kg/day group. Mean stability results of the test material suspension indicated that 4 CPA was stable in when stored for up to 10 days at room temperature.

1. Maternal Toxicity

a. Survival

Except for one dam that died on Day 10 and one dam each sacrificed on Days 9, 10 and 12 at 1000 mg/kg/day no maternal mortality occurred during the study. No treatment-related gross pathological lesions were seen in these dams; all had normally developed implants.

b. Clinical Signs

No treatment-related clinical signs of toxicity were seen at 150 or 300 mg/kg/day. Yellow staining of anogenital haircoat was seen in 2 of 25 dams at 600 mg/kg/day and in 14 of 25 dams at 1000 mg/kg/day. In addition, the animal that was found dead and the three dams that were sacrificed moribund exhibited tremors, uncoordinated movement, recumbent posture, languidness, and cold to touch condition.

c. Body Weight Changes

Mean body weights were significantly decreased only at 1000 mg/kg/day on gestation Days 9, 12, and 16.

Mean body weight gain was statistically significantly decreased in a dose-related manner at 300, 600, and 1000 mg/kg/day during the early dosing period [Days 6-9] and also during the entire dosing period [Days 6-16]. Dams gained weight during the post treatment period [Days 16-20] since the mean body weight gain of treated dams were comparable to that of the controls. For the entire study [Days 0-20], the mean body weight gain was reduced at all dose levels except 150 mg/kg/day; however, the decrease reached statistical significance only at 1000 mg/kg/day.

The mean corrected body weight was 102%, 101%, 99% and 98% of the control value for the 150, 300, 600, and 1000 mg/kg/day groups, respectively.

Dose mg/kg/day	Mean Body Weight Gain [G]					
	Days 0-6	Days 6-9	Days 6-16	Days 16-20	Days 0-20	Net Gain from Day 0
0	40.2	12.6	62.5	65.1	167.9	85
150	39.9	12.1	63.3	68.1	172.1	89
300	41.6	**7.1***	**53.9***	70.2	165.8	87
600	39.1	**0.30***	**51.7***	67.9	158.7	78
1000	40.2	**-10.9***	**42.1***	67.6	**149.1***	78

* = Statistically significantly different from control value.

d. Macroscopical Examination

No treatment-related macroscopical changes were observed in the dams sacrificed at termination.

2. Developmental Toxicity

Reproduction data are presented in Table 1. No biologically or statistically significant effects were seen on pregnancy rate, number of corpora lutea, number of implantations, total live fetuses per litter, resorption rate, number and percent of litters with resorption, or fetal sex ratio. Mean fetal body weights were significantly decreased at 600 and 1000 mg/kg/day. Gravid uterine weights were significantly reduced at 1000 mg/kg/day at any dose level.

Table 1. Cesarean Section Observations

Observations [Mean ± S.D]	Dose Level [mg/kg/day]				
	0	**150**	**300**	**600**	**1000**
No. Assigned	25	25	25	25	25
Females Gravid	25	22	22	25	23
Maternal Wastage					
# Died	0	0	0	0	1
# Sacrificed	0	0	0	0	3
# Aborted	0	0	0	0	0
# Early delivery	0	0	0	0	0
# Non pregnant	0	3	3	0	2
Total Corpora Lutea	404	371	361	423	317
Corpora Lutea/Dam	16.2±2.1	16.9±2.7	16.4±1.8	16.9±2.0	16.7±2.0
Total Implantation	377	347	330	408	296
Implantation/Dam	15±1.0	15.8±3.3	15.0±2.5	16.3±2.3	15.6±1.1
Total Live Fetuses	363	324	312	388	277
Live Fetuses/Litter	14.5±2.2	14.7±3.0	14.2±2.6	15.5±2.5	14.6±1.4
Total Resorptions	14	23	18	20	18
Early	14	23	18	20	16
Late	0	0	0	0	2
Resorptions/Dam	0.6±0.8	1.0±1.0	0.8±0.7	0.8±0.7	0.9±1.0
No. and % of Litters with Resorption	10/25 40	14/22 64	14/22 64	16/25 64	12/19 63
Pre Implantation Loss [%]	6.4±7.4	7.0±10.2	8.3±13.2	3.6±6.1	5.8±8.3
Post Implantation Loss [%]	3.9±5.6	6.3±5.8	5.7±5.7	5.1±4.7	6.4±6.7
Gravid Uterus Weight [g]	83±13	83±16	79±15	81±12	71±9
Sex Ratio ♂ / ♀	51/49	52/48	47/53	49/51	48/52
Covarient Adjusted Fetal Weight [g]	3.8	3.77	3.68	**3.49***	**3.09***

* = Statistically significantly different from control value.

Fetal malformations and variations summarized in Tables 11, 12, and 13 of the study report are appended to this DER. No treatment-related or statistically significant external, visceral, or skeletal malformations were seen in any of the fetuses. The statistically significant, treatment-related skeletal variations observed are summarized below:

			Dose Level [mg/kg/day]				
Skeletal Variations			**0**	**150**	**300**	**600**	**1000**
No. of Litters Examined	L		25	22	22	25	19
No. of Pups Examined	F		184	162	158	193	139
Sternebra(e) Unossified	F	#	24	**33***	**42***	**67***	**112****
		%	13	20	27	35	81
	L	#	13	11	16	**20***	**19***
		%	52	50	73	80	100
Sternebra(e) Misaligned	F	#	0	0	1	1	**6***
		%	0	0	0.6	0.5	4.3
	L	#	0	0	1	1	**4***
		%	0	0	4.5	4.0	21
7th Cervical Rib(s)	F	#	2	2	7	6	**29****
		%	1.1	1.2	4.4	3.1	21
	L	#	2	2	4	5	**10****
		%	8.0	9.1	18	20	53

* = Statistically significantly different from control value.

The fetal incidence for the #5 unossified sternebra at 150 mg/kg/day [33/162] is statistically increased when compared to controls [24/184]; however, the litter incidence [11/22, 50%], is comparable to the concurrent controls [13/25, 52%]. The numerical increase in fetal incidence resulted from 5/8 fetuses from three litters [C79576, C79583 and C79598] and 4/8 fetuses from two litters [C79587 and C79597] having this anomaly compared to 1 or 2 fetuses with this variation in the remaining 6 litters. Since, the litter incidence are comparable to the concurrent controls and the historical controls [range, 0-50%], the numerical increase noted at the low-dose is not considered toxicologically significant. On the other hand, a clear dose-response was observed for this variation for both fetal and litter incidences at doses at and above 300 mg/kg/day, as indicative of a treatment-related effect.

The observance of 7th cervical ribs is also considered to be a treatment-related effect since both the fetal and the litter incidence showed dose-response pattern at 300, 600 and 1000 mg/kg/day, with the increase reaching statistical significance at the high dose. At 1000 mg/kg/day, 4-CPA caused significant increase in the fetal and litter incidence of misaligned sternebra; however, no dose-response was seen.

IV. DISCUSSION

Pregnant rats were given oral administration of 4-CPA at 0, 150, 300, 600 or 1000 mg/kg/day during days 6 through 15 of gestation.

4-CPA at 150 mg/kg/day did not induce maternal toxicity. At 300 mg/kg/day maternal toxicity was limited to significant reductions in body weight gain. At 600 and 1000 mg/kg/day maternal toxicity was manifested by mortality/morbidity [1000 mg/kg/day only], clinical signs of toxicity characterized by yellow staining of the anogenital haircoat, tremors, uncoordinated movement, recumbent posture, languidness, and cold to the touch, and decreases in mean body weights and body weight gains. No treatment related effects were observed in reproductive parameters; there were no significant differences in preimplantation or post implantation loss or in the percent of live fetuses [male, female, and total] or resorptions [early, late, and total]. Covariate-adjusted mean fetal body weights [male, female, and combined] were significantly lower at 600 and 1000 mg/kg/day.

4-CPA did not induce any treatment-related **external, visceral, or skeletal malformations** in any of the fetuses of treated does. **Treatment and/or dose-related fetal skeletal variations included:** increased incidences of **unossified sternebra # 5** at 300, 600 and 1000 mg/kg/day [fetal and litter incidences]; increase in the **seventh cerivical ribs** at 300, 600 and 1000 mg/kg/day [fetal and litter incidence]; and an increase in the incidence of **misaligned sternebrae** at 1000 mg/kg/day [fetal and litter incidences]. No test material-related skeletal malformations were seen.

V. CONCLUSION

4-CPA was maternally toxic to rats at doses of 300, 600 or 1000 mg/kg/day; no maternal toxicity was seen at 150 mg/kg/day. 4-CPA was shown to be a developmental toxin causing decreases in fetal body weights and inducing skeletal variations such as unossified sternebra #5, misaligned sternebra and 7th cervical ribs at doses at and above 300 mg/kg/day; no adverse developmental toxicity was seen at 150 mg/kg/day.

Maternal Toxicity

NOEL = 150 mg/kg/day
LOEL = 300 mg/kg/day

Developmental Toxicity

NOEL = 150 mg/kg/day
LOEL = 300 mg/kg/day

VI. CORE CLASSIFICATION: Guideline; this study satisfies the requirements for a developmental toxicity study in rats [83-3a] and is acceptable for regulatory purposes

TABLE 11
TERATOLOGY STUDY WITH 4-CHLOROPHENOXYACETIC ACID IN RATS
SUMMARY OF FETAL EXTERNAL OBSERVATIONS

HWI 6341101

	DOSE LEVEL	0 MG/KG/DA	150 MG/KG/DA	300 MG/KG/DA	600 MG/KG/DA	1000 MG/KG/DA
Litters Evaluated	N	25	22	22	25	19
Fetuses Evaluated	N	363	324	312	388	278
Live	N	363	324	312	388	277
Dead	N	0	0	0	0	1
M ANAL ATRESIA						
Fetal Incidence	N	0	0	1	0	0
	%	0.0	0.0	0.3	0.0	0.0
Litter Incidence	N	0	0	1	0	0
	%	0.0	0.0	4.5	0.0	0.0
M GENERALIZED EDEMA						
Fetal Incidence	N	0	0	3	0	0
	%	0.0	0.0	1.0	0.0	0.0
Litter Incidence	N	0	0	1	0	0
	%	0.0	0.0	4.5	0.0	0.0
M MICROPHTHALMIA						
Fetal Incidence	N	1	0	0	0	0
	%	0.3	0.0	0.0	0.0	0.0
Litter Incidence	N	1	0	0	0	0
	%	4.0	0.0	0.0	0.0	0.0
M GASTROSCHISIS						
Fetal Incidence	N	1	0	1	0	0
	%	0.3	0.0	0.3	0.0	0.0
Litter Incidence	N	1	0	1	0	0
	%	4.0	0.0	4.5	0.0	0.0
M SHORT THREAD-LIKE TAIL						
Fetal Incidence	N	0	0	1	0	0
	%	0.0	0.0	0.3	0.0	0.0
Litter Incidence	N	0	0	1	0	0
	%	0.0	0.0	4.5	0.0	0.0

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = $P \leq 0.05$; ** = $P \leq 0.01$.
N = Number

TABLE 11
TERATOLOGY STUDY WITH 4-CHLOROPHENOXYACETIC ACID IN RATS
SUMMARY OF FETAL EXTERNAL OBSERVATIONS

HWI 6341101

	DOSE LEVEL	0 MG/KG/DA	150 MG/KG/DA	300 MG/KG/DA	600 MG/KG/DA	1000 MG/KG/DA
Litters Evaluated	N	25	22	22	25	19
Fetuses Evaluated	N	363	324	312	388	278
Live	N	363	324	312	388	277
Dead	N	0	0	0	0	1
TOTAL FETAL EXTERNAL OBSERVATIONS						
Fetal Incidence	N	2	0	5	0	0
	%	0.6	0.0	1.6	0.0	0.0
Litter Incidence	N	2	0	3	0	0
	%	8.0	0.0	14	0.0	0.0

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = $P \leq 0.05$; ** = $P \leq 0.01$.
N = Number

TABLE 12
TERATOLOGY STUDY WITH 4-CHLOROPHENOXYACETIC ACID
IN RATS
SUMMARY OF FETAL SOFT TISSUE OBSERVATIONS

HWI 6341101

	DOSE LEVEL	0 MG/KG/DA	150 MG/KG/DA	300 MG/KG/DA	600 MG/KG/DA	1000 MG/KG/DA
Litters Evaluated	N	25	22	22	25	19
Fetuses Evaluated	N	179	162	154	194	139
Live	N	179	162	154	194	138
Dead	N	0	0	0	0	1
M GASTROSCHISIS						
Fetal Incidence	N	1	0	0	0	0
	%	0.6	0.0	0.0	0.0	0.0
Litter Incidence	N	1	0	0	0	0
	%	4.0	0.0	0.0	0.0	0.0
M MICROPHTHALMIA						
Fetal Incidence	N	3	0	0	1	0
	%	1.7	0.0	0.0	0.5	0.0
Litter Incidence	N	3	0	0	1	0
	%	12	0.0	0.0	4.0	0.0
M FOLDED RETINA						
Fetal Incidence	N	2	0	0	0	0
	%	1.1	0.0	0.0	0.0	0.0
Litter Incidence	N	1	0	0	0	0
	%	4.0	0.0	0.0	0.0	0.0
M HYDROCEPHALY						
Fetal Incidence	N	0	0	0	0	2
	%	0.0	0.0	0.0	0.0	1.4
Litter Incidence	N	0	0	0	0	2
	%	0.0	0.0	0.0	0.0	11
V UNDEVELOPED RENAL PAPILLA						
Fetal Incidence	N	1	0	0	0	0
	%	0.6	0.0	0.0	0.0	0.0
Litter Incidence	N	1	0	0	0	0
	%	4.0	0.0	0.0	0.0	0.0
V DISTENDED URETER(S)						
Fetal Incidence	N	1	0	0	0	1
	%	0.6	0.0	0.0	0.0	0.7
Litter Incidence	N	1	0	0	0	1
	%	4.0	0.0	0.0	0.0	5.3

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = $P<0.05$; ** = $P<0.01$.
N = Number

TABLE 12
TERATOLOGY STUDY WITH 4-CHLOROPHENOXYACETIC ACID IN RATS
SUMMARY OF FETAL SOFT TISSUE OBSERVATIONS

HWI 6341101

DOSE LEVEL		0 MG/KG/DA	150 MG/KG/DA	300 MG/KG/DA	600 MG/KG/DA	1000 MG/KG/DA
Litters Evaluated	N	25	22	22	25	19
Fetuses Evaluated	N	179	162	154	194	139
Live	N	179	162	154	194	138
Dead	N	0	0	0	0	1
TOTAL FETAL SOFT TISSUE OBSERVATIONS						
Fetal Incidence	N	7	0*	0*	1*	3
	%	3.9	0.0	0.0	0.5	2.2
Litter Incidence	N	5	0	0	1	3
	%	20	0.0	0.0	4.0	16

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = $P \leq 0.05$; ** = $P \leq 0.01$.
N = Number

TABLE 13
TERATOLOGY STUDY WITH 4-CHLOROPHENOXYACETIC ACID IN RATS
SUMMARY OF FETAL SKELETAL OBSERVATIONS

BWI 6341101

DOSE LEVEL		0 MG/KG/DA	150 MG/KG/DA	300 MG/KG/DA	600 MG/KG/DA	1000 MG/KG/DA
Litters Evaluated	N	25	22	22	25	19
Fetuses Evaluated	N	184	162	158	193	139
Live	N	184	162	158	193	139
Dead	N	0	0	0	0	0
M SACRAL CENTRA ABSENT						
Fetal Incidence	N	0	0	1	0	0
	%	0.0	0.0	0.6	0.0	0.0
Litter Incidence	N	0	0	1	0	0
	%	0.0	0.0	4.5	0.0	0.0
M CAUDAL VERTEBRA(E) ABSENT						
Fetal Incidence	N	0	0	1	0	0
	%	0.0	0.0	0.6	0.0	0.0
Litter Incidence	N	0	0	1	0	0
	%	0.0	0.0	4.5	0.0	0.0
V STERNEBRA(E) UNOSSIFIED						
Fetal Incidence	N	24	33*	42**	67**	112**
	%	13	20	27	35	81
Litter Incidence	N	13	11	16	20*	19**
	%	52	50	73	80	100
V MISALIGNED STERNEBRA(E)						
Fetal Incidence	N	0	0	1	1	6**
	%	0.0	0.0	0.6	0.5	4.3
Litter Incidence	N	0	0	1	1	4*
	%	0.0	0.0	4.5	4.0	21
V RUDIMENTARY RIB(S)						
Fetal Incidence	N	4	7	13*	5	8
	%	2.2	4.3	8.2	2.6	5.8
Litter Incidence	N	2	6	7	4	2
	%	8.0	27	32	16	11
V 7TH CERVICAL RIB(S)						
Fetal Incidence	N	2	2	7	6	29**
	%	1.1	1.2	4.4	3.1	21
Litter Incidence	N	2	2	4	5	10**
	%	8.0	9.1	18	20	53

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05; ** = P<0.01.
N = Number

TABLE 13
TERATOLOGY STUDY WITH 4-CHLOROPHENOXYACETIC ACID
IN RATS
SUMMARY OF FETAL SKELETAL OBSERVATIONS

HWI 6341101

DOSE LEVEL		0 MG/KG/DA	150 MG/KG/DA	300 MG/KG/DA	600 MG/KG/DA	1000 MG/KG/DA
Litters Evaluated	N	25	22	22	25	19
Fetuses Evaluated	N	184	162	158	193	139
Live	N	184	162	158	193	139
Dead	N	0	0	0	0	0
V SKULL BONE(S) UNOSSIFIED						
Fetal Incidence	N	4	1	3	1	2
	%	2.2	0.6	1.9	0.5	1.4
Litter Incidence	N	3	1	2	1	2
	%	12	4.5	9.1	4.0	11
V SKULL BONE(S) REDUCED IN OSSIFICATION						
Fetal Incidence	N	2	0	0	1	2
	%	1.1	0.0	0.0	0.5	1.4
Litter Incidence	N	2	0	0	1	2
	%	8.0	0.0	0.0	4.0	11
M CERVICAL ARCH(ES) FUSED						
Fetal Incidence	N	0	0	1	0	0
	%	0.0	0.0	0.6	0.0	0.0
Litter Incidence	N	0	0	1	0	0
	%	0.0	0.0	4.5	0.0	0.0
V GREATER THAN 26 PRESACRAL VERTEBRA(E)						
Fetal Incidence	N	0	0	2	0	0
	%	0.0	0.0	1.3	0.0	0.0
Litter Incidence	N	0	0	1	0	0
	%	0.0	0.0	4.5	0.0	0.0
M SACRAL CENTRA ASYMMETRIC						
Fetal Incidence	N	0	0	1	0	0
	%	0.0	0.0	0.6	0.0	0.0
Litter Incidence	N	0	0	1	0	0
	%	0.0	0.0	4.5	0.0	0.0
M SACRAL ARCH(ES) ABSENT						
Fetal Incidence	N	0	0	1	0	0
	%	0.0	0.0	0.6	0.0	0.0
Litter Incidence	N	0	0	1	0	0
	%	0.0	0.0	4.5	0.0	0.0

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = $P \leq 0.05$; ** = $P \leq 0.01$.
N = Number

TABLE 13
TERATOLOGY STUDY WITH 4-CHLOROPHENOXYACETIC ACID IN RATS
SUMMARY OF FETAL SKELETAL OBSERVATIONS

HWI 6341101

DOSE LEVEL		0 MG/KG/DA	150 MG/KG/DA	300 MG/KG/DA	600 MG/KG/DA	1000 MG/KG/DA
Litters Evaluated	N	25	22	22	25	19
Fetuses Evaluated	N	184	162	158	193	139
Live	N	184	162	158	193	139
Dead	N	0	0	0	0	0
V UNILATERAL FULL RIB						
Fetal Incidence	N	0	0	1	0	0
	%	0.0	0.0	0.6	0.0	0.0
Litter Incidence	N	0	0	1	0	0
	%	0.0	0.0	4.5	0.0	0.0
M FUSED RIB(S)						
Fetal Incidence	N	0	0	0	0	1
	%	0.0	0.0	0.0	0.0	0.7
Litter Incidence	N	0	0	0	0	1
	%	0.0	0.0	0.0	0.0	5.3
V BENT RIBS						
Fetal Incidence	N	0	1	0	0	1
	%	0.0	0.6	0.0	0.0	0.7
Litter Incidence	N	0	1	0	0	1
	%	0.0	4.5	0.0	0.0	5.3
V PELVIC BONE(S) REDUCED IN OSSIFICATION						
Fetal Incidence	N	0	1	0	0	1
	%	0.0	0.6	0.0	0.0	0.7
Litter Incidence	N	0	1	0	0	1
	%	0.0	4.5	0.0	0.0	5.3
TOTAL FETAL SKELETAL OBSERVATIONS						
Fetal Incidence	N	35	43	55**	75**	121**
	%	19	27	35	39	87
Litter Incidence	N	18	14	18	22	19*
	%	72	64	82	88	100

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = $P<0.05$; ** = $P<0.01$.
N = Number

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